II. REMARKS

A. Status of the Claims

At the time of the Office Action, claims 1-5, 8-9, 11, 14-15, 20-23, 26, 28-29, and 31 were pending in the case, with claims 6-7, 10, 12-13, 16-19, 24-25, 27, 30, and 32 having been withdrawn as being directed to a non-elected invention. Claims 3-5, 8, 14, 15, 20, 23, 26, 28, 29, and 31 been amended in the Amendment set forth herein. Claims 1-2, 9, 11, and 33-43 have been canceled without prejudice or disclaimer. New claims 44-55 have been added. Thus, claims 3-5, 8, 14, 15, 20-23, 26, 28, 29, 31, and 44-55 are currently under consideration in the case.

Regarding the amendment of claim 3, it has been amended to be in independent form and to recite a genus of non-natural amino acids. New claims 44-55 individually recite the non-natural amino acids set forth in the genus of non-natural amino acids in claim 3. Support for the amendment of claim 3 and the new claims can be found generally throughout the specification, such as in the claims as originally filed and in the following sections of the specification: Table 2 (page 21, line 7 – page 24, line 4); page 50, line 25 – page 51, line 23 – page 52, line 28; and Table II, page 64, lines 1-2.

Claim 14 has been amended to recite "identifying the CTL epitope of the antigen prior to substituting the at least a first amino acid." Support for this amendment can be found generally throughout the specification, such as on page 25, line 3 – page 26, line 22, particularly lines 9-11.

B. The Objections to the Specification Are Overcome

The specification is objected to because it is said to contain embedded hyperlinks and/or other forms of browser-executable code. The Examiner has specifically cited to the Table legend on page 65 of the specification. Applicants have amended this Table as well as other sections of

the specification to omit any embedded hyperlinks and/or other forms of browser-executable code. Therefore, the objection to the specification has been overcome.

Applicants make note of the Examiner's comments concerning the incorporation of essential material in the specification by reference to unpublished U.S. applications, foreign applications or patents, and publications. Applicants have reviewed the specification to determine whether material incorporated by reference is non-essential or essential.

The drawings are objected to because they contain handwritten text. Applicants concurrently file herewith corrected drawing sheets in compliance with 37 C.F.R. 1.121(d).

C. Comments Regarding Information Disclosure Statement

The Examiner notes that references A1, A3, and A4 as set forth in the previously submitted Information Disclosure Statement do not appear to be related to the subject matter of the present patent application. The Information Disclosure Statement indicates that A1 is U.S. Patent 4,433,092 (Nemeth). However, there is a typographical error in the patent number. The patent that should have been cited is U.S. Patent 4,833,092 (Geyson). Applicants concurrently file herewith a supplemental Information Disclosure Statement that sets forth this reference. The specification has also been amended to correct the typographical error.

Regarding A3, the previously submitted Information Disclosure Statement indicates that A3 is U.S. Patent 4,631,221 (Disselbeck and Stahl). However, there is a typographical error in the patent number. The patent that should have been cited is U.S. 4,631,211 (Houghton). Applicants concurrently file herewith a supplemental Information Disclosure Statement that sets forth this patent.

Regarding A4, the previously submitted Information Disclosure Statement indicates that A4 is U.S. Patent 4,708,781 (Poorten). However, there is a typographical error in the patent number. The patent that should have been cited is U.S. patent 4,708,871 (Geysen). Applicants concurrently file herewith a supplemental Information Disclosure Statement that sets forth this patent. Further, the specification has also been amended to correct the typographical error.

D. The Rejections Under 35 U.S.C. §112, Second Paragraph, Are Overcome

Claims 9 and 14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse.

Claim 9 is alleged to be indefinite for reciting "wherein the first substitute amino acid reduces one $-CH_2/CH_3$ group on the side chain." Without conceding that the Examiner is correct, Applicants note that this issue is moot because claim 9 has been canceled without prejudice or disclaimer.

Claim 14 is alleged to be indefinite for reciting "further comprising determining the CTL epitope of the antigen" because it is not clear what is meant. Without conceding that this claim is indefinite, Applicants note that claim 14 has been amended to recite "further comprising identifying the CTL epitope of the antigen prior to substituting the at least a first amino acid." The specification provides substantial detail regarding the identification of CTL epitopes (*see, e.g.*, specification, page 25, line 3 – page 26, line 22). Further, the claim as written makes it clear that such identification occurs prior to the amino acid substitution. Support for this limitation is as discussed above, particularly in the specification at page 25, lines 4-16. In view of the foregoing, the indefiniteness rejection of claim 14 under 35 U.S.C. §112, first paragraph, has been overcome and Applicants respectfully request withdrawal of this rejection.

E. The Rejections Under 35 U.S.C. §102 Are Moot or Overcome

1. Rejections Based on Gillogly as Evidenced by Castilleja

Claims 1, 4, 5, 11, 14, 20-22, 28, and 29 are rejected under 35 U.S.C. §102(b) as being anticipated by Gillogly *et al.* (FASEB J. 14:A147.18, 2000; C19 in the IDS; hereinafter "Gillogly") as evidenced by Castilleja *et al.* (J. Immunol. 2002, 169:3545-3554, IDS reference; hereinafter "Castilleja"). Gillogly is said to teach making a panel of CTL peptide epitope variants of "E75" (KIFGSLAFL). Castilleja is cited as teaching that the S5K variant is a weaker agonist than the unaltered peptide. Thus, Gillogly as evidenced by Castilleja is said to anticipate the claimed invention. Applicants respectfully traverse.

Without conceding that the claims as originally written would have been anticipated by Gillogly as evidenced by Castilleja, Applicants note that claim 3, a claim which was not included in this rejection, was amended to be in independent form, and the dependencies of claims 4, 5, 14, 20-23, 28, and 29 changed to depend from claim 3 instead of claim 1. Claims 1 and 11 have been canceled without prejudice or disclaimer. Further, new claims 44-55 each depend from claim 3, and are therefore not considered anticipated. Therefore, the rejection under 35 U.S.C. §102(b) based on Gillogly as evidenced by Castilleja is moot. While Gillogly and Castilleja use natural amino acids with dramatic increases or decreases in energy, the present application uses only unnatural amino acids with discrete controllable small changes in energy. Such small and discrete changes cannot be accomplished with natural amino acids.

2. Rejections Based on Baker

Claims 1, 3, 4, 5, 8, 14, 15, 23, and 31 are rejected under 35 U.S.C. §102(b) as being anticipated by Baker *et al.* (Immunity, 2000, 13:475-484, IDS reference; hereinafter "Baker"). Baker is said to teach making analog peptides of the HTLV-1 peptide epitope LLFGYPVYV, the analogs being LLFGYAVYV and further position 6 analogs that utilize the non-natural amino

acid residues N-ethyl glycine, N-methyl glycine, and N-propyl alanine to modulate TCR binding and signaling, and that this disclosure anticipates the claims. Applicants respectfully traverse.

As discussed above, claim 3 as amended now recites that the first substitute amino acid is a non-natural amino acid "selected from the group consisting of γ-aminobutyric acid, norvaline, norleucine, isophenylalanine, phenyl glycine, homolysine, γ-methyl_l-leucine, homophenylalanine, 2-amino 2-hydroxy acetic acid, homoserine, homoleucine, and ornithine." Baker fails to anticipate claim 1, or any of its dependent claims because it does not expressly or inherently disclose any of the specific non-natural amino acids set forth in claim 1. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). Further, Baker does not anticipate any of new claims 44-55 because Baker does not expressly or inherently disclose any of the recited non-natural amino acids in these claims. Baker uses unnatural amino acids which have methyl ethyl, and propyl groups covalently linked to the NH_2 group. The present application uses methylene (not methyl) incorporated into the side chain and the terminal amino group remains free.

In view of the foregoing, none of the pending claims are anticipated by Baker under 35 U.S.C. §102(b). Therefore, it is respectfully requested that the rejection of the claims under 35 U.S.C. §102(b) based on Baker be withdrawn.

3. Rejections Based on WO 01/36452

Claims 1, 2, 4, 5, 8, 14, 20-23, 26, and 29 are rejected under 35 U.S.C. §102(a) as being anticipated by WO 01/36452 (of record). WO 01/36452 is said to teach heterocyclic analogs of p53.261 that were more potent at inducing higher avidity CTL against the native wild-type

epitope than the wild-type peptide itself. WO 01/36452 is also said to teach heterocyclic analogs of certain MHC class I binding peptide epitopes. The Examiner argues that the disclosure of WO 01/36452 anticipates the claimed invention. Applicants respectfully traverse.

Without conceding that the claims as originally written would have been anticipated by WO 01/36452, Applicants note that independent claim 3 has been amended to be in independent form, and to recite a genus of non-natural amino acids. Claim 3 was not included in the rejection, and was thus not considered to be anticipated by WO 01/36452. Further, each of the remaining claims depend from claim 3 and are thus not anticipated. In addition, new claims 44-55 are not anticipated by WO 01/36452 because each of these claims depends from claim 3, which for the foregoing reasons is not anticipated by WO 01/36452. Therefore, the rejection of the claims under 35 U.S.C. §102(b) as being anticipated by WO 01/36452 is moot.

F. The Rejections Under 35 U.S.C. §103(a) Are Overcome

Claims 1, 4, 5, 11, 14, 15, 20-22, 28, and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gillogly (discussed above) in view of Fisk *et al.* (J. Exp. Med. 1995, 181:2109-2117, IDS reference; hereinafter "Fisk") and Madden *et al.* (Cell. 1993, 75:693-708, IDS reference; hereinafter "Madden"). Applicants respectfully traverse.

Applicants note that claim 3 was not included in this rejection, thus indicating that the Examiner considered claim 3 to be nonobvious in view of Gillogly in view of Fisk and Madden. As discussed above, claim 3 has been amended to be in independent form, and dependencies of remaining pending claims changed to depend from claim 3 Further, new claims 44-55 each depend from claim 3 and would thus also be considered nonobvious. See *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.")

In view of the foregoing, the pending claims are not unpatentable under 35 U.S.C. §103(a) over Gillogly in view of Fisk and Madden. Therefore, it is respectfully requested that the rejection of the claims under 35 U.S.C. §103(a) based on Gillogly in view of Fisk and Madden be withdrawn.

G. Requirement for Information under 37 C.F.R. §1.105

The Examiner has provided an attached requirement for information under 37 C.F.R. §1.105 with the Office Action. The requirement concerns a request for information regarding the presentation related to the Gillogly *et al.* abstract discussed above. In particular, the Examiner has requested a copy of the poster, if one was presented, or a statement describing all of the data that was presented on the poster or in an oral presentation. Applicant is also being asked to furnish a statement describing any additional presentations and/or abstracts presented by Applicants at scientific meetings wherein data pertinent to the subject matter was discussed, and the contents of such disclosure. Applicants attach as Exhibit 1 the Declaration of Dr. Constantin G. Ioannides, one of the inventors and a co-author of the Gillogly *et al.* abstract, who has provided a statement regarding the requested information.

H. Conclusion

The foregoing is believed to be a complete response to the Office Communication dated July 9, 2008. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: March 6, 2009

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Constantin G. Ioannides *et al*

Serial No.: 10/507,009

Filed: March 28, 2005

For: CONTROLLED MODULATION OF AMINO ACID SIDE CHAIN LENGTH OF PEPTIDE ANTIGENS

Group Art Unit: 1644

Examiner: Dibrino, Marianne NMN

Atty. Dkt. No.: UTSC:711US

Confirmation No.: 7673

DECLARATION OF DR. CONSTANTIN G. IOANNIDES

I, Dr. Constantin G. Ioannides, hereby declare as follows:

1. I am a USA citizen residing at 4062 Tartan Lane , Houston, Texas , 77025-2919, USA.

2. I am an inventor of the subject matter claimed in the above-referenced patent application.

3. I am submitting this declaration to provide information regarding the Examiner's request for information about the presentation related to the abstract by Gillogly *et al* ("Induction of Immunity to HER-2 by TCR Directed Variants of the CTL epitope E75," *FASEB J.*, 14:A 147. 18, 2000). I am a co-author of the Gillogly abstract and was head of the laboratory.

4. The Gillogly abstract concerns a poster presentation that was presented about nine years ago at FASEB meeting. The poster was discarded after poster presentation. A copy of the actual poster could not be located by me or any of the co-authors of the abstract, and thus is not available.

EXHIBIT 1

5. The poster concerned studies describing the testing of a panel of E75-variants with whole natural amino acid replacements in candidate positions to contact TCR. The contact of TCR was illustrated by ability of the variants containing the whole natural amino acid replacements in to stimulate IFN-γ induction in healthy donor PMBCs. The results presented described three E75 variants modified at presumed CDR3 contacts.

6. Regarding the F42 variant mentioned in the abstract (abbreviated as S5K), F42 has serine replaced with lysine (lysine has a positive charge and is thus electrostatic compared to serine). Another peptide variant mentioned in the abstract, F46, is F8K. The replacement involved the replacement of phenyl-alanine with lysine. Lysine in both F42 and F46 induces an electrostatic charge in the epitope at positions 5 and 8. The charge equals 10 and 100 times stronger forces than of Ser 5 and of Phe 8, respectively. A third peptide was used, however the authors of the poster do not recollect the precise variant. None of the peptide variants evaluated included addition or removal of a methylene group. (The methylene groups are not charged, the forces of the methylene group are van der Waals). The van der Walls forces are 10 times weaker than the H-bond forces found in the Ser.

7. I do not know if the information was presented by Gillogy or anybody else in other meetings. Gillogly left my laboratory in the fall of 2001. I was not at that meeting and to my knowledge none of the other authors of the poster were at the meeting.

8. I hereby declare that all statements made by my own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such

willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date 03/05/2009

C. G. Ioannides

Dr. Constantin G. Ioannides